REMARKS

Claims 1, 3-5, 7, 8, 10-14, 16, 17, 21-36, 38, and 42-44 were pending in the application, with claims 42 and 43 withdrawn from present consideration. Claims 42 and 43 are presently withdrawn. Upon entry of these amendments, Claims 1, 3-5, 7, 8, 10-14, 16, 17, 21-36, 38, and 42-44 will be pending and under active consideration. Claims 1, 32, 33, 42, and 43 are independent.

Applicants respectfully request entry of the remarks made herein into the file history of the present invention. Reconsideration and withdrawal of the rejections set forth in the above-identified Office Action are respectfully requested.

I. The Rejections Under 35 U.S.C. § 112(2nd) Should Be Withdrawn

At pages 2-3 of the Office Action, claims 32 and 34-36 were rejected as allegedly failing to particularly point out and distinctly claim the subject matter which the Applicants regard as their invention. In particular, the Office Action alleges that the metes and bounds of the term "remote" are not clearly stated. Applicants traverse respectfully.

Respectfully, Applicants submit that "remoteness" is a characteristic of systems and networks that is well understood by those skilled in the art. The term "remote" is a subjective term, and thus its precise meaning is dependent upon the context in which it is used. In view of this inherent subjectivity and the common understanding and application of the term by those skilled in the art, Applicant wishes to avoid being bound to any single definition for "remote." Notwithstanding the above, "remote" means separate from, not physically connected to, or in a different location from an object or place that is referred to as being remote.

Claim 33 stands rejected as allegedly being unclear on the basis that executable computer code cannot perform some of the functions cited in the claim. Applicants traverse respectfully. In claim 33, the transitional term "comprising" refers to the "system" and not to the "code." The system is capable of performing all of the cited functions.

Claim 38 is rejected for allegedly being "entirely unclear" as to its metes and bounds on the basis that an infection cannot be identified before it occurs. Applicants traverse respectfully. Claim 38 recites, "wherein infected patients are identified prior to an outbreak of the bacterial infection." Clearly, the claim provides that it is the patients who are identified prior to the outbreak, not the infection. Regardless, patients who have an infection are potential sources of an outbreak. The presently claimed invention provides a means whereby an infectious agent may be identified and the source of that infectious agent may be quarantined or otherwise rendered safe to others prior to the occurrence of an outbreak.

Claim 44 is rejected for allegedly failing to further limit the system of claim 32. Applicants traverse respectfully. Claim 44 adds the limitation, absent in claim 32, of "transmitting the sequence data to the server over a computer network."

In view of the above, Applicants request respectively that the rejections under 35 U.S.C. § 112(second paragraph) be withdrawn.

II. The Rejections Under 35 U.S.C. § 103(a) Should Be Withdrawn

A. The Allegations and Deficiencies

Claims 1, 3-5, 7, 8, 10-14, 16, 17, 21-36, 38, and 44, variously, stand rejected under 35 U.S.C. § 103(a) as allegedly being obvious over CDC Plan "Preventing Emerging Infectious Diseases; a Strategy for the 21st Century, October, 1998" (hereinafter, "CDC Plan 1998") in view of Frothingham *et al.*, "Genetic Diversity in the Mycobacterium tuberculosis Complex

Based on Variable Numbers of Tandem DNA Repeats," *Microbiology* 144:1189-96 (1998) (hereinafter, "Frothingham") or in view of van Belkum *et al.*, "Short-Sequence DNA Repeats in Prokaryotic Genomes," *MMBR* 62:275-293 (1998) (hereinafter, "van Belkum 1998"). Applicants traverse respectfully.

The Examiner alleges, in sum, that CDC Plan 1998 discloses methods of tracking and controlling infectious diseases via the systematic collection, analysis, interpretation, and dissemination of health data through a network. The collected data is allegedly used by epidemiologists to detect outbreaks, characterize disease transmission patterns by time, place, and person, and provide warnings based on the analysis. Specifically, the Office Action alleges that CDC Plan 1998 meets steps 1-6 and the "warning step" (step 8) of Applicants' claimed method, arguing that "[t]he collection of samples meets step (1) of the method. The analysis and interpretation encompasses steps (2-4) of the method. Detecting the outbreak and characterization meet the limitations of steps (5 and 6) and the dissemination meets the 'warning' step of the claimed method." (Office Action at pages 3-4.) The Office Action further alleges that CDC Plan 1998 teaches that "molecular fingerprinting techniques" are to be used in the analysis, such techniques to include comparing sequences and comparing sizes of fragments.

Respectfully, Applicants take issue with the Office Action's broad characterizations of the teachings of CDC Plan 1998 with respect to Applicants' claims. As noted above, the Office Action alleges that the generic descriptions in CDC Plan 1998 teach or suggest all of the elements found in steps (1-6 and 8) of Applicants' claimed method. However, the Office Action fails to address specific elements of those steps, and in doing so the Office Action appears to rely heavily on the knowledge that one skilled in the art of infection control systems would have had at the time the application was filed. In particular, the Office Action's allegation that molecular

fingerprinting techniques, as known by those skilled in the art at the time of the invention, included comparison of sequence data on a base pair level and a motif level is unsupported. Applicants submit respectfully (as will be discussed more thoroughly below) that novel elements of Applicants' claimed method were *not* known by those skilled in the art at the time of the application (apart from the inventors), and only through impermissible hindsight reconstruction can Applicants' invention be derived from the cited references.

The Office Action, at pages 5-6, acknowledges that CDC Plan 1998 fails to teach the sequencing of VNTR regions of bacteria. However, the Office Action alleges that Frothingham cures this deficiency by teaching the sequencing of the VNTR region of pathogens and comparing the presence, size, and sequence of these regions between samples to measure the diversity of and identify pathogen strains. The Office action, at pages 6-9, admits that CDC Plan 1998 fails to teach or suggest sequencing VNTR regions, specifically those in the protein A or coagulase genes of *S. aureus*, and also fails to teach or suggest sequencing multiple regions of DNA. However, the Office Action alleges that van Belkum 1998 cures these deficiencies by teaching that genetic diversity in pathogens may be assessed by sequencing the VNTR regions of pathogens, specifically those in the protein A or coagulase genes of *S. aureus*, and comparing the presence, size, and sequence of these regions between samples to measure the diversity of and identify pathogen strains. Applicants strongly disagree with these characterizations of the cited references.

Applicants submit respectfully that the novel system and method for tracking and controlling infections of the present invention is neither taught nor suggested by CDC Plan 1998, either alone or in combination with Frothingham or van Belkum 1998. In particular, and without acquiescing the propriety of the other allegations made in the Office Action, there is neither

teaching nor suggestion found within the combination of these references and the knowledge of one skilled in the art at the time of the application for 1) comparing VNTR sequence data of at least two samples on both a base pair level and a repeat motif level, or 2) using that sequence comparison to measure the phylogenetic relatedness between the compared samples. Applicants submit respectfully that these novel elements of Applicants' claimed method are not disclosed within the combination of the cited references nor were they know to those skilled in the art at the time of the application (apart from the inventors).

B. The Combination of CDC Plan 1998 with Frothingham

With regard to the Office Action's allegation that the combination of CDC Plan 1998 with Frothingham teaches or suggests all of the elements of claims 1, 3-5, 8, 10-14, 16, 17, 21-27, 32-36, 38, and 44 (with Frothingham curing the deficiencies or CDC Plan 1998 as described above), Applicants submit respectfully that Frothingham does not teach or suggest sequencing DNA as a method of molecular fingerprinting. Frothingham merely describes another application of the traditional length-based molecular fingerprinting technique such as those found in previously-cited references Applicants have refuted in prior responses to Office Actions in this matter.

Although Frothingham discloses the act of DNA sequencing, Frothingham fails to disclose the comparison of sequence data between pathogens as a method of identifying and characterizing those pathogens. (It should be noted here that Applicants do not deny that DNA sequencing was known in 1998, but rather that DNA sequencing was not used in the novel and patentable manner as recited and described in Applicants' claims at that time.) Frothingham clearly discloses a *DNA size-based* analysis of the pathogens studied. In Table 1, column 4 (page 1190), Frothingham discloses the DNA sequence of the PCR primers *only* and does not teach

that the DNA sequence of entire VNTR regions was acquired or analyzed. In table column 5, Frothingham displays the length and number of repeats. In Table 1, column 6, Frothingham discloses the overall length of the PCR product which would include the VNTR region in addition to the regions flanking the VNTR region, to which the PCR primers bind. Tables 2 and 3 clearly display the *number* of tandem repeats and not their DNA sequence. Figures 2 and 3 display the *image-based* (not sequence-based) result that displays the *length* (*i.e.,* size) of the DNA fragment.

The "Methods" based section of Frothingham describes searching a published *M. tuberculosis* genome (H37Rv sequence from Sanger Centre) to find repeat location. This does not constitute sequencing DNA from a plurality of bacteria nor comparing sequences on a base pair level and a motif level. In the "Methods - PCR and Sequencing" section, Frothingham describes an *image-based* system that determines the *length* of a DNA fragment but not its actual DNA sequence, stating "[t]he presence and size of each PCR product was determined by electropheresis on an agarose gel in Tris/boric acid/EDTA buffer followed by staining with ethidium bromide." The results of this test are displayed in Figures 2 & 3. It is this image-based, length determining method that Frothingham uses as a molecular typing tool.

Applicants acknowledge that Frothingham does describe *limited* DNA sequencing, but this sequencing method and the sequence data provided thereby are *not* used for the purpose of molecular typing–the sequence data were used merely to confirm that the correct PCR product was obtained for the size-based analysis (otherwise Frothingham would teach direct DNA sequencing of *all* the bacterial isolates in this paper rather than only selected isolates). On page 1192, in section "PCR Product Sequencing", Frothingham teaches that "[w]e sequenced PCR products from some loci to confirm that our PCR products corresponded to the expected

regions." Clearly, this sequence data was not used for a base pair level and motif level analysis of VNTR regions from different organisms. Frothingham continues "Sequence analysis of multiple PCR products in the MPTR-A and ETR-A loci also confirmed that *length* polymorphisms corresponded to insertion or deletion of complete tandem repeat units." Thus, Frothingham performed limited DNA sequencing to confirm his length based image molecular typing tests.

Even further, Frothingham acknowledges that his molecular typing method is not sequence based. At page 1194, in "Applications of VNTR Strain Typing" section, Frothingham teaches that "VNTR typing is the standard method for human forensic and paternity testing and may be useful for bacterial typing...VNTR typing *by PCR* has several advantages...." As was well known to one skilled in the art at the time of the invention, VNTR typing by PCR describes an image-based length determining technique and *NOT* an analysis based on actual sequencing of DNA. While the Office Action uses the term "VNTR sequencing" to describe Frothingham's disclosed method in the context "One skilled in the art would have been motivated to have incorporated the VNTR sequencing of Frothingham...", which implies that the Frothingham performed direct DNA sequencing as a molecular typing, Frothingham in fact repeatedly uses the phrase "VNTR typing" and not "VNTR sequencing" to describe his own method; the Office Action's usage is inappropriate.

Therefore, there is nothing in Frothingham that, when combined with the 1998 CDC plan, teaches or suggests Applicants' claimed invention.

C. The Combination of CDC Plan 1998 with Van Belkum 1998

With regard to the Office Action's allegation that the combination of CDC Plan 1998 with van Belkum 1998 teaches or suggests all of the elements of claims 1, 3-5, 7, 8, 10-14, 16,

17, 21-36, 38, and 44 (with van Belkum 1998 curing the deficiencies or CDC Plan 1998 as described above), Applicants submit respectfully that van Belkum 1998 does not teach or suggest sequencing VNTR DNA as a method of assessing genetic diversity of a pathogen. In fact, Applicants submit respectfully that van Belkum 1998 merely describes yet another version of the classical DNA fingerprinting analysis, which is based on electrophoretic determination of the *sizes* of DNA fragments generated in a number of ways (including PCR and restriction length polymorphism analysis (RFLP)) and *not* on any analysis of the DNA sequence of VNTR regions. (Applicants point out respectfully at this point that the Office has cited numerous references in opposition to the present claims, and all of those have been shown by Applicants, as we show here, to utilize size-based analysis and not sequence analysis--this is because, despite whatever may *seem* obvious in the year 2006, those skilled in the art in 1998 (other than the inventors) *were not using* sequence-bases analyses of VNTR regions on a base pair level and a motif level, but rather were using size-based analyses in molecular fingerprinting. Despite what may seem obvious in 2006, Applicants' invention was novel at the crucial time of the invention.)

Van Belkum 1998 does not cure the deficiencies of CDC Plan 1998 with respect to DNA sequence analysis because van Belkum 1998's method is just another example of a size-based method. The Office Action states that van Belkum "obtain[s] patient samples and sequence[s] the VNTR region of protein A and/or coagulase gene of *S. aureus*. (See pages 283-284)." (Office Action at page 8.) Applicants respectfully request that the Examiner point out specifically the passages describing the sequencing of the noted regions, as Applicants find only disclosure of *protein* sequences and PCR/RFLP analysis. For example, on page 284, in the *S. aureus* section, Frothingham teaches that repeat sequences "can be visualized by combined PCR and restriction length polymorphism analysis. The assay can be used for epidemiological

research." As there is not disclosure of methods that involve sequencing the VNTR regions, this teaching is contrary to the allegation made in the Office Action that Frothingham teaches that "[p]rimers can be used to amplify the VNTR, then its size *and sequence* are determined." (Office Action at page 8.)

The Office Action continues by stating that van Belkum 1998 "note[s] the successful use of PCR mediated SSR amplification, followed by size study and using sequencing for the pathogens *H. influenzae* and *C. albicans*." In fact, the passage from van Belkum 1998 that is apparently paraphrased by the Examiner in the quote above, found at page 287, bottom of the right column, actually teaches that the "[s]uccessful use of PCR-mediated SSR amplification followed by amplicon size determination [used] to analyze the spread of microbial pathogens has been reported for *H. influenzae* and *C. albicans*." (Citations removed.) Likewise, at, van Belkum 1998 teaches that "at page 286, bottom of the left column, teaches that "[b]y *PCR mediated amplification* of the repeats, all potential SSRs were shown to be polymorphic among strains."(Emphasis added.) Thus, contrary to the Office Action's allegation, van Belkum 1998 teaches only size-based methods of analysis for this pathogen. Although Van Belkum 1998 does state at page 287 that "automated DNA sequencing" was used in the *H. influenzae* and *C. albicans* studies, van Belkum 1998 teaches that it was used "for the determination of allelic polymorphisms and for precise size determination," thus confirming that the analysis was focused on size discrimination and RFLP analysis rather than comparison of DNA sequences on a base pair level and motif level as required under Applicants' claims.

Accordingly Applicants submit respectfully that there is nothing in van Belkum 1998 that cures the deficiencies of CDC Plan 1998 with respect to Applicants' claims.

D. Conclusion of Arguments

Thus, Applicants submit respectfully that, as neither Frothingham nor van Belkum 1998 cure the deficiencies of CDC Plan 1998 with respect to the claims of the present invention, and as the combination of the cited references thus fails to teach or suggest all of the elements of Applicants' claims, the combination of the cited references fails to meet the threshold required for establishing a *prima facie* case of obviousness under 35 U.S.C. § 103(a). Accordingly, Applicants submit respectfully that the rejection of claims 1, 3-5, 7, 8, 10-14, 16, 17, 21-36, 38, and 44 under 35 U.S.C. § 103(a) have been traversed, and Applicants request respectfully that the rejection of claims 1, 3-5, 7, 8, 10-14, 16, 17, 21-36, 38, and 44 under 35 U.S.C. § 103(a) be withdrawn.

AUTHORIZATION

Applicants believe there is no fee due in connection with this filing other than the fee for three month's extension of time to file this response (which fees are authorized on the accompanying request). However, to the extent required, the Commissioner is hereby authorized to charge any fees due in connection with this filing to Deposit Account 19-5127 (Order No. 4191240002) or credit any overpayment to same.

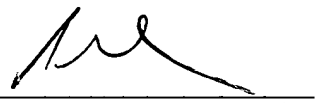
CONCLUSION

Applicants submit respectfully that the present application is in condition for allowance. Favorable reconsideration, withdrawal of the rejections set forth in the above-noted Office Action, and an early Notice of Allowance are requested.

If the Examiner feels that an interview would facilitate the prosecution of this application, Applicants respectfully urge the Examiner to contact the undersigned directly at 202-373-6116.

In general, Applicants' undersigned attorney may be reached in our Washington, D.C. office by telephone at (202) 424-7500. All correspondence should be directed to our address given below.

Respectfully submitted,



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